activate endothelial cells may provide novel treatment strategies for ischemic AKI.

DISCLOSURES

None.

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See related article, "Vascular-Resident CD169-Positive Monocytes and Macrophages Control Neutrophil Accumulation in the Kidney with Ischemia-Reperfusion Injury," on pages 896–906.

Understanding the Role of Rituximab in ANCA GN: Regressing toward the Mean

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Who in their right mind could argue? It made complete pathogenetic sense that remission induction could be accomplished by rituximab-induced depletion of circulating peripheral CD20-positive B cells in patients with ANCA vasculitis. ANCAs are bioindicators of inflammatory autoimmune conditions affecting small vessels, namely granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic GPA. Since the initial discovery of ANCAs directed against myeloperoxidase (MPO) and/or proteinase 3, there has been an explosion of insight into pathogenetic disease mechanisms that has directly led to novel therapeutic inroads.[1] For example, ANCAs bind to and activate circulating neutrophils, thereby resulting in vascular inflammation, and the murine model of MPO-ANCA vasculitis revealed that ANCAs are necessary and sufficient to cause and perpetuate disease.[2,3] As with the use of plasma exchange to physically remove offending ANCAs, this compendium of data made a very strong case from a pathogenetic standpoint that the use of rituximab to deplete peripheral B cells would be beneficial. Furthermore, maintenance of this effect could be long lasting. In other words, ridding the inflammatory milieu of the etiologic stimulant could melt disease. It should be noted that this rituximab-induced melting is not instantaneous—it takes time. Rituximab is unable to deplete plasmablasts and plasma cells, because these cells do not harbor CD20 on their cell surface and are known to reside outside of the circulation; thus, ANCA titers fall slowly over time in individuals treated with rituximab.[4–6] Unfortunately, kidney involvement is exceedingly common in GPA and MPA and typified by pauci-immune, necrotizing, and crescentic GN. The degree and duration of kidney involvement before treatment portend a worse prognosis, suggesting that glomeruli suffer until ANCAs are removed for good.[7]

It came as no surprise that both patients with ANCA vasculitis and their health care providers were enthusiastic about

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the promise of using rituximab to induce remission. Soon after the use of rituximab in case reports and series, the results of the Rituximab for ANCA-Associated Vasculitis (RAVE) Trial revealed that induction of remission using concomitant rituximab and corticosteroids was noninferior to oral cyclophosphamide and corticosteroids followed by azathioprine at the 6-month mark in patients with newly diagnosed or relapsing disease.[4] Notably, subjects were excluded from the trial if they had an entry creatinine>4.0 mg/dl, alveolar hemorrhage requiring mechanical ventilation, and/or previous exposure to plasma exchange or cyclophosphamide within the past 3 or 4 months. Complete remission was similarly achieved in both groups at 6 months (61% versus 63% in the rituximab and cyclophosphamide groups, respectively), and roughly 75% of patients in both groups achieved complete remission before the 18-month mark. Moreover, time from complete remission to relapse was not significantly different between the two groups. The 18-month follow-up results showed that the efficacy of a single induction dosing regimen of rituximab in the presence of corticosteroids was as effective as the alternative immunosuppressive regimen and significantly superior at 6 and 12 months (P value=0.01 and P value=0.009, respectively) in patients with relapsing disease at baseline.[5] Unfortunately, a sustained remission rate in either arm of <40% was truly disappointing, especially given the reported higher remission rates in prior trials of similar duration.[8,9]

We must put these findings into the context of important messages that arose from the contemporary Rituximab Versus Cyclophosphamide in ANCA-Associated Vasculitis (RITUXVAS) Trial, which compared rituximab, corticosteroids, and two intravenous cyclophosphamide pulses (administered at weeks 0 and 2) with corticosteroids and 3–6 months of intravenous cyclophosphamide followed by azathioprine in patients with newly diagnosed ANCA vasculitis who had kidney involvement.[6] Participants had more severe kidney involvement (median eGFRs of 20 and 12 ml/min per 1.73 m^2 in the rituximab and control groups, respectively) than their RAVE Trial counterparts at baseline. Sustained remission at the 12-month mark, defined as Birmingham Vasculitis Activity Score=0 for 6 months or more, was achieved in 25 (76%) participants in the rituximab group and 9 (82%) participants in the control group (P=0.68). Overall, the treatment regimen using rituximab was not superior. The take-home message at the end of the day in 2010 from both of these trials was that rituximab was equivalent to its comparator; it was not better, and it was not worse.

What is the role of rituximab in the treatment of ANCA vasculitis? Rituximab can work to induce remission in patients with mild to moderate kidney involvement, but we must still remember that it is equivalent to cyclophosphamide. The notion that we can relegate patients with a serum creatinine≤4.0 mg/dl to receive rituximab and corticosteroids is useful for clinical trial purposes, but it is inappropriate for practicing clinicians to apply this metric in real-world settings. For example, the rapidity with which eGFR declines at or near presentation, regardless of the actual value, is a guidepost that many seasoned clinicians would use to provide aggressive immunosuppression beyond rituximab. Even more importantly, we should not use rituximab, because we think it is a kinder and gentler immunosuppressant. The numbers of total adverse events (2051 and 2819 adverse events by 6 and 18 months, respectively), serious adverse events, and non-disease related adverse events were similar in both arms of the RAVE Trial.[4,5] Interestingly, this similarity in adverse events was also observed in the RITUXVAS Trial.[6] We must conclude, using results from well conducted clinical trials in the field, that the adverse event profile for rituximab- or cyclophosphamide-based remission induction regimens is no different. These similarities in adverse events seem perplexing given that rituximab specifically depletes only CD20-positive B cells from the circulation, whereas cyclophosphamide, an alkylating agent that crosslinks DNA strands, thereby decreasing DNA synthesis, casts a much larger and less specific cytotoxic net. Additionally, we must also remember that the long-term safety of rituximab use in humans is limited compared with that of cyclophosphamide.

If rituximab is not better or safer and may take longer to work, what is the best and most durable remission induction therapy for patients with severe ANCA GN? For now, we must rely on the outcomes of the RITUXVAS Trial and trust that patients with severe ANCA GN (defined as those patients with kidney involvement whose eGFR is severely reduced and/or rapidly worsening) should receive corticosteroids and cyclophosphamide at a minimum. In addition, short-term outcomes data from the MEPEX Trial suggest that any patient with severe kidney involvement (defined in the trial as a serum creatinine>5.8 mg/dl) could benefit from the addition of plasma exchange to their induction regimen. End

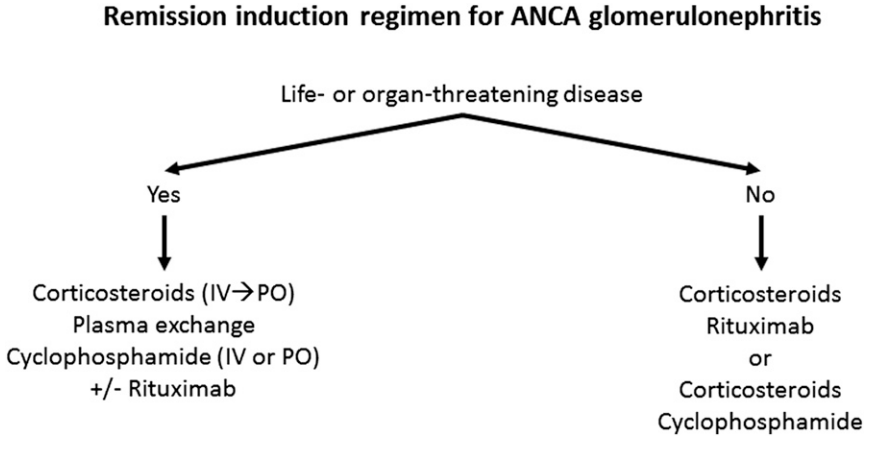

Figure 1. Algorithm to determine appropriate remission induction regimen for ANCA glomerulonephritis based on disease severity. IV, intravenous; PO, oral.

stage kidney disease-free survival was significantly improved at the 3-month mark in the participants of the MEPEX Trial who received seven plasma exchanges versus 3000 mg intravenous methylprednisolone (69% versus 49%, respectively; $P=0.02$) in addition to oral cyclophosphamide and prednisone.[10] Unfortunately, this benefit did not persist over time[11]; however, the most recent meta-analysis of plasma exchange for ANCA GN suggested that this intervention may decrease end stage kidney disease or death.[12] The Plasma Exchange and Glucocorticoid Dosing in the Treatment of Antineutrophil Cytoplasmic Autoantibody-Associated Vasculitis Trial is now underway in an attempt to solidly answer this question (clinicaltrials.gov identifier NCT00987389). With these published data in hand, we propose the following treatment algorithm for the management of patients with severe ANCA GN (Figure 1).

Ultimately, remission induction with oral or intravenous cyclophosphamide and corticosteroids followed by rituximab to maintain remission might be the right approach for severe disease. Two recent retrospective series provide evidence for this latter regimen, and we eagerly await the results of the Maintenance of Remission Using Rituximab in Systemic ANCA-Associated Vasculitis Trial (clinicaltrials.gov identifier NCT00748644) and the Rituximab Versus Azathioprine as Remission Maintenance Therapy in ANCA Vasculitis Trial (clinicaltrials.gov identifier NCT01697267).[13,14] We should also closely examine whether immunosuppression could be stopped indefinitely in select individuals who are in long-term remission.

In this issue of *JASN*, we have a good example of the use of rituximab for ANCA vasculitis with mild to moderate kidney involvement.[15] A *post hoc* analysis of the RAVE Trial outcomes after 18 months was conducted among 102 (52%) evenly divided participants who had kidney involvement. The majority of this subset also had GPA ($n=68$; 67%) and was proteinase 3 ANCA-positive ($n=58$; 57%). Outcomes of patients with either biopsy-proven ANCA GN or clinically diagnosed kidney involvement were similar; however, it should be noted that kidney involvement was biopsy-proven in only 45 (44%) participants.

How can we do better? These prior experiences tell us that there is still room in the field for novel agents. Until a clinical trial is conducted to identify the best induction regimen for severe ANCA GN, including one in which an adequate number of patients with MPA and/or MPO ANCA seropositivity are enrolled, it is likely that excitement surrounding the short- and long-term results of the RAVE Trial will begin to regress toward the mean over time. Rituximab, similar in efficacy and safety to standards of care in appropriate circumstances, now serves as another steadfast vine in the therapeutic jungle of ANCA vasculitis.

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DISCLOSURES

None.

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See related article, "Rituximab Versus Cyclophosphamide for ANCA-Associated Vasculitis with Renal Involvement," on pages 976–985.

β-Blockers in Dialysis Patients: A Nephrocardiology Perspective

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β-Blockers are the most commonly prescribed cardiovascular medications among dialysis patients, constituting 64% of all prescriptions.[1] However, the evidence supporting their utility in improving cardiovascular outcomes in this population is conflicting. Data from the US Renal Data System (USRDS) identified β-blockers as the only antihypertensive agents independently associated with a reduced hazard of adjusted all-cause mortality in a large sample of dialysis patients in the United States,[2] but observational data from Ontario, Canada, demonstrated no beneficial effects on cardiovascular outcomes among older dialysis patients.[3] Agarwal and colleagues performed a randomized analysis of lisinopril versus atenolol (each administered three times a week) among a predominantly black hemodialysis population, not only overcoming the limitations of prior observational studies but also comparing two commonly used agents.[4] Although not powered for mortality outcomes, the study was stopped prematurely because of important safety concerns about cardiovascular outcomes in the lisinopril group.

In this context, the study by Weir and colleagues in this issue of *JASN*[5] represents an "a-ha" moment, promising an intriguing pivot from the existing literature. The observational design means that any conclusions must be considered strictly hypothesis generating. Yet the study underscores the fact that not all β-blockers can be considered equal and that it would be a mistake to lump them together as one class for future analysis in the dialysis population. Despite the several caveats and limitations, this study brings into the limelight the glimmer of a possible association with a survival advantage of certain β-blockers simply based on their pharmacokinetic behavior during dialysis. There is an inherent inclusion/survival bias because only dialysis patients older than 65 years of age were studied (to ensure consistent identification of all patients with prescription drug coverage in Ontario), thus excluding patients with premature cardiovascular mortality who presumably have the highest prevalence of vasculopathy.

The low-dialyzability β-blocker of great interest that unfortunately could not be studied by Weir *et al.* is carvedilol. This, admittedly, is due to the existing prescription characteristics of β-blockers in Ontario ("carvedilol use limited to patients with echocardiographic/symptomatic evidence of advanced heart failure"[5]). Carvedilol has shown substantial promise in this population on the basis of translational as well as clinical evidence. Among patients with intradialytic hypertension, carvedilol in high doses is associated with improved endothelial function (flow-mediated vasodilation) and better intradialytic and interdialytic BP control.[6] Carvedilol is also the only β-blocker with a demonstrated survival advantage in a randomized controlled trial (RCT) among dialysis patients with dilated cardiomyopathy.[7] Critics may argue that a single RCT is insufficient to derive generalizable conclusions; regrettably, the academic community has yet to produce another RCT to investigate benefits in this high-risk population. Therefore, it is with the highest enthusiasm that we look forward to the Beta-blocker to LOwer CArdiovascular Dialysis Events (BLOCADE) trial, a randomized placebo-controlled trial that has been planned to assess the role of carvedilol in reducing cardiovascular morbidity and mortality in high-risk patients receiving dialysis (Australian and New Zealand Clinical Trials Registry number: ACTRN12609000174280). On the basis of the study design, we anticipate that high-risk patients for whom β-blocker therapy should already be recommended under existing practice guidelines (*e.g.*, symptomatic systolic heart failure, uncontrolled hypertension) may not be included in the trial (making enrollment particularly challenging); however, safety and tolerability are the primary objectives of this ambitious feasibility trial.

Given the marked heterogeneity of β-blockers, it would be rather naive to assume that dialyzability is the sole factor responsible for benefits noted or should be clinicians' sole consideration

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